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=> s interleukin-6
      3204 INTERLEUKIN
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L1     322 INTERLEUKIN-6
           (INTERLEUKIN(W)6)

=> s l1 and rheumatoid arthritis
      5327 RHEUMATOID
      8900 ARTHRITIS
      4757 RHEUMATOID ARTHRITIS
           (RHEUMATOID(W)ARTHRITIS)
L2      90 L1 AND RHEUMATOID ARTHRITIS

=> s l2 and antagonist#
     11246 ANTAGONIST#
L3      22 L2 AND ANTAGONIST#

=> s l3 and treat?
    512760 TREAT?
L4      22 L3 AND TREAT?

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1. 5,641,657, Jun. 24, 1997, DNA encoding an **interleukin**-**6** splice variant; Steven Ruben, et al., 435/69.52, 252.3, 320.1, 325, 348, 358, 365.1, 419; 530/351; 536/23.5 [IMAGE AVAILABLE]

2. 5,635,533, Jun. 3, 1997, Methods for inducing differentiation of a cell using phenyacetic acid and derivatives; Dvorit Samid, 514/538, 563, 567 [IMAGE AVAILABLE]

3. 5,635,532, Jun. 3, 1997, Compositions and methods for therapy and prevention of pathologies including cancer, AIDS and anemia; Dvorit Samid, 514/538, 563, 567; 560/19 [IMAGE AVAILABLE]

4. 5,605,930, Feb. 25, 1997, Compositions and methods for **treating** and preventing pathologies including cancer; Dvorit Samid, 514/510, 513, 515, 529, 538, 563, 567 [IMAGE AVAILABLE]

5. 5,599,708, Feb. 4, 1997, Osteoclast growth regulating factors and antibodies; Gregory R. Mundy, et al., 435/331; 424/138.1, 145.1, 155.1, 174.1, 178.1, 185.1, 198.1; 435/70.2, 172.2, 336; 530/326, 388.24, 389.1, 413 [IMAGE AVAILABLE]

6. 5,591,827, Jan. 7, 1997, **Interleukin**-**6** receptor **antagonists**; Just P. J. Brakenhoff, et al., 530/351; 424/85.2; 435/69.52; 930/141 [IMAGE AVAILABLE]

7. 5,571,513, Nov. 5, 1996, Anti-gp130 monoclonal antibodies; Samuel A. Burstein, 424/144.1, 153.1, 173.1; 435/70.21, 172.2, 334; 530/387.1, 388.22, 388.7, 388.85, 389.6, 391.3 [IMAGE AVAILABLE]

8. 5,559,012, Sep. 24, 1996, Therapeutic, IL-6 antibody kits, and process for their preparation; Herve Brailly, et al., 435/70.21; 424/145.1; 530/388.23 [IMAGE AVAILABLE]

9. 5,545,623, Aug. 13, 1996, Method of inhibiting secretion of inflammatory cytokines; Akira Matsumori, 514/26; 536/5 [IMAGE AVAILABLE]

10. 5,527,546, Jun. 18, 1996, Human **interleukin** **6** inhibitor; Delia E. Penza, et al., 424/573 [IMAGE AVAILABLE]

11. 5,521,315, May 28, 1996, Olefin substituted long chain compounds; Gail Underiner, et al., 546/243; 544/285; 546/242 [IMAGE AVAILABLE]

12. 5,519,000, May 21, 1996, Tumor necrosis factor inhibitors; George A. Heavner, et al., 514/12, 13, 14; 15, 16, 17, 18; 530/324, 326, 328, 329, 330 [IMAGE AVAILABLE]

13. 5,506,340, Apr. 9, 1996, Tumor necrosis factor inhibitors; George A. Heavner, 530/324, 325, 326, 327, 328, 329, 330 [IMAGE AVAILABLE]

14. 5,504,108, Apr. 2, 1996, Optically pure 4-aryl-2-hydroxytetronic acids; Donald T. Witiak, et al., 514/473; 549/315, 316 [IMAGE AVAILABLE]

15. 5,486,595, Jan. 23, 1996, Tumor necrosis factor inhibitors; George A. Heavner, 530/324, 325, 326, 327, 328, 329, 330 [IMAGE AVAILABLE]

16. 5,484,726, Jan. 16, 1996, Antibodies specific for human stromelysin-3 and a method for detection of stromelysin-3; Paul Basset, et al., 435/7.4; 530/387.1, 387.7, 388.1, 388.26, 388.8 [IMAGE AVAILABLE]

17. 5,468,772, Nov. 21, 1995, Tripterinin compound and method; Ren S. Xu, et al., 514/453, 825; 549/275, 281 [IMAGE AVAILABLE]

18. 5,420,109, May 30, 1995, Cytokine restraining agents; Mark J. Suto, et al., 514/8, 16, 17, 18; 530/317, 322, 328, 329, 330 [IMAGE AVAILABLE]

19. 5,310,742, May 10, 1994, Uses for thioureylenes; Alan N. Elias, 514/274 [IMAGE AVAILABLE]

20. 5,210,075, May 11, 1993, **Interleukin** **6** **antagonist** peptides; Wolfgang Scholz, et al., 514/14, 13, 15; 530/326, 327, 328 [IMAGE AVAILABLE]

21. 5,209,920, May 11, 1993, Evaluative means for detecting inflammatory reactivity; Esther M. Sternberg, et al., 435/7.92; 206/569; 424/85.1, 85.2, 85.4, 85.5, 85.6, 85.7; 435/975; 436/2, 506; 514/805, 825, 885, 886, 889 [IMAGE AVAILABLE]

22. 5,006,330, Apr. 9, 1991, Evaluative means for detecting inflammatory reactivity; Esther M. Sternberg, et al., 436/506; 514/2, 21, 825 [IMAGE AVAILABLE]

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U.S. Patent & Trademark Office LOGOFF AT 10:52:22 ON 18 JUL 1997

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=> s interleukin-6 or il-6

L1 12445 FILE MEDLINE
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L4 13414 FILE SCISEARCH

TOTAL FOR ALL FILES
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=> s l5 and rheumatoid arthritis

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L9 576 FILE SCISEARCH

TOTAL FOR ALL FILES
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=> s l10 and antagonist#

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L12 27 FILE EMBASE
L13 19 FILE BIOSIS
L14 49 FILE SCISEARCH

TOTAL FOR ALL FILES
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=> s l15 and treat?

L16 9 FILE MEDLINE
L17 8 FILE EMBASE
L18 5 FILE BIOSIS
L19 14 FILE SCISEARCH

TOTAL FOR ALL FILES
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L26 23 DUP REM L20 (13 DUPLICATES REMOVED)

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L26 ANSWER 1 OF 23 MEDLINE
TI The effects of traditional antirheumatic herbal medicines on immune response cells.
AU Chang D M; Chang W Y; Kuo S Y; Chang M L
SO JOURNAL OF RHEUMATOLOGY, (1997 Mar) 24 (3) 436-41.
Journal code: JWX. ISSN: 0315-162X.
AB OBJECTIVE: Clinically, some traditional Chinese herbal medicines have been thought to be effective in ***treating*** rheumatic diseases such as ***rheumatoid*** ***arthritis*** and systemic lupus erythematosus. To examine the mechanism by which such herbal remedies might be effective, we investigated the ability of Tripterygium wilfordii Hook-f (TWHf) and tetrandrine (TTD) to affect human immune responsiveness in vitro. METHODS: We measured the ability of these agents to affect cytokine secretion from monocytes or T cells, prostaglandin E2 (PGE2) secretion from monocytes, IgG production from B cells, and the phagocytosis of bacteria by neutrophils. RESULTS: These studies revealed that both TWHf and TTD significantly inhibited interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), ***IL*** - ***6*** , and IL-8 secretion from monocytes, IgG secretion from B cells, and phagocytosis of bacteria by neutrophils; however, only TWHf inhibited IL-2 and IL-4 production from lymphocytes, and PGE2 secretion from monocytes. CONCLUSION: TWHf and TTD exert a powerful suppressive effect on human immune responses. This action might account for their therapeutic effectiveness in rheumatic diseases, and might support broader and more rigorous clinical trials.

L26 ANSWER 2 OF 23 MEDLINE DUPLICATE 1
TI Modulation of cytokine production by human mononuclear cells following impairment of Na, K-ATPase activity.
AU Foey A D; Crawford A; Hall N D
SO BIOCHIMICA ET BIOPHYSICA ACTA, (1997 Jan 10) 1355 (1) 43-9.
Journal code: A0W. ISSN: 0006-3002.
AB Cytokines, including TNF alpha and IL-l beta, are central to the chronic inflammatory process and tissue damage that characterises diseases such as ***rheumatoid*** ***arthritis*** . The mechanisms responsible for long-term generation of these molecules are poorly understood. We have previously demonstrated impaired activity of Na, K-ATPase, a key enzyme regulating intracellular cation levels, on rheumatoid mononuclear cells. Mimicking this 'defect' on normal mononuclear cells with ouabain has been shown to induce TNF alpha and, in particular, IL-l beta production, whereas ***IL*** - ***6*** synthesis was suppressed. A similar pattern of cytokine generation was noted when mononuclear cells were ***treated*** with the sodium ionophore, monensin. Induction of cytokine production was related to up-regulation of the appropriate mRNA, although enhanced secretion of processed IL-l beta was also observed. The mechanism underlying these cellular responses appears to involve sodium/calcium exchange across the cell membrane. Impaired Na,K-ATPase activity might promote pro-inflammatory cytokine secretion in patients with ***rheumatoid*** ***arthritis*** .

L26 ANSWER 3 OF 23 MEDLINE
TI Inhibition of superantigen-induced proinflammatory cytokine production and inflammatory arthritis in MRL-lpr/lpr mice by a transcriptional inhibitor of TNF-alpha.
AU Edwards C K 3rd; Zhou T; Zhang J; Baker T J; De M; Long R E; Borcherding D R; Bowlin T L; Bluethmann H; Mountz J D
SO JOURNAL OF IMMUNOLOGY, (1996 Aug 15) 157 (4) 1758-72.
Journal code: IFB. ISSN: 0022-1767.
AB We have used fas-defective MRL-lpr/lpr mice to study the effects of the staphylococcal enterotoxin superantigens on the development of autoimmune, inflammatory joint disease in animals that are susceptible to the development of ***rheumatoid*** ***arthritis*** -like disease. We show that systematic administration by a single i.p. injection of staphylococcal enterotoxin B (SEB; 10 micrograms/mouse) caused a mild, inflammatory arthritis +30 days postchallenge in the knee joints of young (< 2-mo-old) MRL-lpr/lpr mice, but not aged-matched MRL +/+ mice. In aged (> 8-mo-old) MRL-lpr/lpr mice, but not in aged MRL +/+ mice,

SEB caused a severe, inflammatory arthritis, as assessed histologically, and systemic autoimmune disease, including glomerulonephritis and autoantibody production. Furthermore, in aged MRL-lpr/lpr mice, SEB but not heat-denatured SEB caused acute weight loss and elevated levels of serum proinflammatory cytokines. Compared with highly purified peritoneal macrophages obtained from either aged MRL +/+, young MRL-lpr/lpr, or young MRL +/+, peritoneal macrophages obtained from aged MRL-lpr/lpr mice constitutively expressed 2- to 10-fold greater levels of TNF-alpha, IL-1 beta, ***IL*** - ***6*** , and IL-10, and produced elevated amounts of these cytokines when ***treated*** in vitro with SEB. SEB-challenged aged MRL-lpr/lpr mice ***treated*** with anti-TNF mAb (100 micrograms/mouse; every other day), anti-V beta 8 TCR mAb (250 micrograms/mouse; every other day), or orally with the novel TNF-alpha inhibitor MDL 201,449A (9-[(1R, 3R)-trans-cyclopentan-3-ol] adenine; 25 mg/kg/day) exhibited reduced inflammatory arthritis, autoantibody formation, and serum TNF-alpha levels, but not IL-10 levels, after +30 days of ***treatment*** . These data suggest that SEB is an extremely potent macrophage-activating factor in vitro and in vivo, enhancing several aspects of autoimmune disease in MRL-lpr/lpr mice, and that anti-TNF therapies may have potential use in inflammatory arthritis.

L26 ANSWER 4 OF 23 MEDLINE
TI In vivo blockade of TNF-alpha by intravenous infusion of a chimeric monoclonal TNF-alpha antibody in patients with ***rheumatoid*** ***arthritis*** . Short term cellular and molecular effects.
AU Lorenz H M; Antoni C; Valerius T; Repp R; Grunke M; Schwerdtner N; Nusslein H; Woody J; Kalden J R; Manger B
SO JOURNAL OF IMMUNOLOGY, (1996 Feb 15) 156 (4) 1646-53. Journal code: IFB. ISSN: 0022-1767.
AB Due to the unknown etiology of RA, specific ***treatment*** is not available. Recently, in a double-blinded, placebo-controlled clinical trial, in vivo blockade of TNF-alpha by a single infusion of a chimeric TNF-alpha-blocking mAb, cA2, has proven to be highly effective in the ***treatment*** of RA. In parallel to this trial, we tested the consequences of cA2 infusion in ex vivo and in vitro experiments. In this paper, we describe an increase in CD4+ and CD8+ T lymphocyte counts on day 1 and a marked decrease in monocyte counts preferentially on day 7 after cA2 ***treatment*** , without major changes in B lymphocyte or NK cell counts. In addition, we found an increased responsiveness of PBMC to CD28 mAb/PMA, but not to CD3 mAb, superantigen staphylococcus enterotoxin B, or PHA on day 1 after infusion. The increase in DNA synthesis of PBMC was paralleled by increased IL-2 mRNA and IL-4 mRNA expression and IL-2 protein secretion in culture supernatants after in vitro stimulation of PBMC with CD28 mAb/PMA. In PBMC, we did not find any significant changes in mRNA or protein expression of CD28 Ag or CD28 ligands, B7-1 and B7-2. Serum concentrations of IL-1 beta, ***IL*** - ***6*** , and soluble CD14 were significantly diminished after in vivo TNF-alpha blockade. We did not see relevant changes in granulocyte function in vitro after cA2 infusion. Finally, we observed a statistically significant decrease in sICAM-1 molecules in the serum of patients ***treated*** with verum compared with that in the serum of subjects given placebo. This change in sICAM-1 concentration was evident on days 1 and 7 after the infusion of 10 mg/kg cA2, whereas it occurred only on day 7 in the serum of patients ***treated*** with the low dose (1 mg/kg) of cA2.

L26 ANSWER 5 OF 23 MEDLINE
TI Induction of cytokines and ICAM-1 by proinflammatory cytokines in primary rheumatoid synovial fibroblasts and inhibition by N-acetyl-L-cysteine and aspirin.
AU Sakurada S; Kato T; Okamoto T
SO INTERNATIONAL IMMUNOLOGY, (1996 Oct) 8 (10) 1483-93. Journal code: AY5. ISSN: 0953-8178.
AB The role of transcription factor NF-kappa B in the induction of cytokines and ICAM-1 upon stimulation with proinflammatory cytokines, IL-1 and tumor necrosis factor (TNF)-alpha was investigated in primary synovial fibroblasts obtained from patients with ***rheumatoid*** ***arthritis*** (RA). Nuclear translocation of NF-kappa B was demonstrated after 30 min of ***treatment*** with IL-1 or TNF-alpha. Thereafter, the production of several cytokines including granulocyte macrophage colony stimulating factor, ***IL*** - ***6*** and IL-8, that are known to be abundantly produced in the synovial cavity of RA patients, was greatly augmented. Similarly, cell surface expression of ICAM-1 was induced by the IL-1 or TNF-alpha ***treatment*** . Since expression of these genes is induced in rheumatoid synovial tissue, this experimental system is considered to represent the in vivo situation of RA pathophysiology. Using this cell culture system we attempted to modulate the intracellular signaling cascade for NF-kappa B activation and examined the effects of N-acetyl-L-cysteine (NAC) and acetylsalicylic acid (aspirin), which were previously reported to inhibit NF-kappa B activation. Pretreatment of the primary synovial fibroblasts with NAC inhibited nuclear translocation of NF-kappa B. Subsequently, the induction of these cytokines and ICAM-1 was considerably suppressed. On the other hand, pretreatment with aspirin blocked these phenomena only partially. These observations indicate the pivotal role of NF-kappa B in RA pathogenesis thus highlighting the possibility of a novel therapeutic strategy.

L26 ANSWER 6 OF 23 SCISEARCH COPYRIGHT 1997 ISI (R)
TI DIFFERENTIAL EXPRESSION OF MACROPHAGE INFLAMMATORY PROTEIN-2 AND MONOCYTE CHEMOATTRACTANT PROTEIN-1 IN EXPERIMENTAL GLOMERULONEPHRITIS
AU TAM F W K (Reprint); KARKAR A M; SMITH J; YOSHIMURA T; STEINKASSERER A; KURRLE R; LANGNER K; REES A J
SO KIDNEY INTERNATIONAL, (MAR 1996) Vol. 49, No. 3, pp. 715-721. ISSN: 0085-2538.
AB We examined the relation between glomerular expression of chemokines from alpha-subfamily (macrophage inflammatory protein-2, MIP-2) and beta-subfamily (monocyte chemoattractant protein-1, MCP-1) and infiltration of neutrophils and monocytes in antibody mediated glomerulonephritis in rats. In the accelerated model of nephrotoxic nephritis (NTN), glomerular expression of MIP-2 and MCP-1 genes correlated with the sequential migration of neutrophil and monocyte influx, respectively. These relationships were investigated further in the heterologous phase of NTN by applying various ***treatments*** known to modulate the severity of injury. Pretreatment with bacterial lipopolysaccharide resulted in greater injury, MIP-2 expression increased 25- to 50-fold, and the glomerular neutrophil count increased two- to fourfold. Both MIP-2 mRNA levels and neutrophil infiltration were reduced by additional pretreatment with ***IL*** - ***6*** , IL-1 receptor ***antagonist*** , soluble IL-1 receptor or soluble TNF receptor (Spearman correlation coefficient $r = 0.897$, $P < 0.005$). In the heterologous phase of NTN, different pre- ***treatments*** only resulted in trivial changes in MCP-1 expression and monocyte infiltration. In conclusion, glomerular MIP-2 gene expression correlates with neutrophil infiltration both temporally during the evolution of nephritis, and when glomerular injury is modified by ***treatment*** . Glomerular MCP-1 gene expression correlates with monocyte influx. The data show chemokines of alpha- and beta-subfamilies co-operative to cause selective and sequential migration of different leukocyte subsets during development of antibody mediated glomerulonephritis.

L26 ANSWER 7 OF 23 SCISEARCH COPYRIGHT 1997 ISI (R)
TI MECHANISMS OF LOSS OF LEAN BODY-MASS IN PATIENTS ON CHRONIC DIALYSIS
AU DINARELLO C A (Reprint); ROUBENOFF R A
SO BLOOD PURIFICATION, (SEP/OCT 1996) Vol. 14, No. 5, pp. 388-394. ISSN: 0253-5068.
AB Patients on chronic dialysis ***treatment*** often have reduced lean body mass. Certain aspects of bio-incompatibility in dialysis can be viewed as leading to a chronic inflammatory state, In most chronic inflammatory diseases, loss of mean body mass is independent of reduced caloric intake, However, reduced caloric intake accounts for most of the weight loss in these patients and also dialysis patients, Refeeding is associated with increased fat deposition more than restoration of muscle mass, In addition to reduced caloric intake, patients with ***rheumatoid*** ***arthritis*** , a classic example of a chronic inflammatory disease, have an elevated resting energy expenditure associated with

decreased lean body mass. Elevated cellular tumor necrosis factor (TNF) and IL-1 beta production can be demonstrated in these patients. However, in many dialysis patients, increased cytokine production can be 'normal' or reduced. This takes place as the level of malnutrition increases. Thus, cytokines such as IL-1 and TNF play a decreasing role in the pathogenesis of loss of body mass as malnutrition increases and curtails the synthesis of cytokines, Similar to patients with AIDS, progressive disease in patients on chronic dialysis may exhibit subclinical malnutrition which leads to decreased cytokine production, Reduction in cytokine production can be viewed as a protective mechanism.

L26 ANSWER 8 OF 23 MEDLINE
TI The Chinese herbal remedy, T2, inhibits mitogen-induced cytokine gene transcription by T cells, but not initial signal transduction.
AU Tao X; Davis L S; Hashimoto K; Lipsky P E
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1996 Jan) 276 (1) 316-25.
Journal code: JP3. ISSN: 0022-3565.
AB T2, an extract of Tripterygium wilfordii Hook F, has been reported to be effective in the ***treatment*** of a variety of autoimmune diseases, including ***rheumatoid*** ***arthritis*** . Previous studies have shown that T2 inhibited mitogen- or antigen-induced proliferation of human peripheral blood T cells and B cells, IL-2 production by T cells and Ig production by B cells. In contrast, T2 did not affect monocyte functions, such as IL-1 production and antigen presentation. The current studies sought to localize the immunosuppressive action of T2 more precisely. Results show that T2 prevented [3H]-uridine uptake by mitogen-stimulated T cells and arrested them in the early GI phase of the cell cycle. The inhibitory effects of T2 could be partially overcome by costimulating PHA activated T cells with PMA and completely nullified by costimulation with PMA plus a monoclonal antibody to CD28. Moreover, T2 had no effect on expression of IL-2R or the transferrin receptor (CD71), but inhibited production of a number of cytokines, including IL-2 and IFN-gamma by activated T cells. T2 suppressed IL-2 mRNA levels, but not IL-2R mRNA levels, in activated T cells. T2-mediated inhibition reflected suppression of IL-2 gene transcription as indicated by suppression of the expression of a reporter gene driven by the IL-2 promoter. T2 had little inhibitory effect on either IL-2 gene expression or cell cycle progression when added after initial mitogenic stimulation, indicating that an early step in the cascade of activation events was inhibited. However, initial activation events including protein tyrosine phosphorylation, the generation of diacylglycerol, IP3, and the translocation of protein kinase C were not inhibited by T2. Moreover, T2 did not inhibit the phosphatase activity of calcineurin. These results have localized the effect of T2 to a step in the T cell activation cascade after initial second messenger generation, tyrosine phosphorylation and protein kinase activation, but before IL-2 gene transcription.

L26 ANSWER 9 OF 23 SCISEARCH COPYRIGHT 1997 ISI (R)
TI EFFECT OF IL-10 ON COLLAGEN-INDUCED ARTHRITIS IN MICE
AU TANAKA Y; OTSUKA T (Reprint); HOTOKEBUCHI T; MIYAHARA H; NAKASHIMA H; KUGA S; NEMOTO Y; NIIRO H; NIHO Y
SO INFLAMMATION RESEARCH, (JUN 1996) Vol. 45, No. 6, pp. 283-288.
ISSN: 1023-3830.
AB In the present study we investigated the effect of a potent anti-inflammatory cytokine, interleukin (IL)-10, on the development of collagen-induced arthritis (CIA) in mice. Each DBA1/J mouse was immunized with 200 mu g of native collagen and followed by booster injections at 3 weeks. rmIL-10 was injected i.p. daily at a dose of 100 ng/mouse. Mice were divided into four groups according to the administration period of rmIL-10. As a result, a 48-day course of IL-10 ***treatment*** significantly suppressed the severity of arthritis. Among the 4 groups, the most pronounced suppression was observed in the group in which IL-10 was given from day 0 to 21. On the other hand, there were no significant differences in the serum IgG anti-type II collagen (CII) titers between the four groups. Moreover, the production of cytokines (***IL*** - ***6*** and tumor necrosis factor-alpha (TNF-alpha)) and other mediators (prostaglandin E2 (PGE2) and nitric oxide (NO)) by peritoneal macrophages seemed to show no clear correlation with the severity of arthritis in mice. These results raise the possibility that IL-10 might be a useful agent for suppressing the progression and the development of CIA in mice.

L26 ANSWER 10 OF 23 SCISEARCH COPYRIGHT 1997 ISI (R)
TI EFFECT OF TUMOR-NECROSIS-FACTOR ANTIBODY ON SYNOVIAL-FLUID CYTOKINE ACTIVITIES IN EQUINE ANTEBRACHIOCARPAL JOINTS INJECTED WITH ENDOTOXIN
AU HAWKINS D L (Reprint); CARGILE J L; MACKAY R J; BROOME T A; SKELLEY L A
SO AMERICAN JOURNAL OF VETERINARY RESEARCH, (OCT 1995) Vol. 56, No. 10, pp. 1292-1299.
ISSN: 0002-9645.
AB Six horses received intra-articular injections of a mixture of 1 mu g of endotoxin/5 mg of equine tumor necrosis factor (eqTNF) monoclonal antibody in 1 antebrachiocarpal joint and an equal volume (2 ml) of 1 mu g of endotoxin/5 mg of control antibody in the opposite joint. Synovial fluid sample collection (1 ml) was accomplished by use of an indwelling, intra-articular catheter at postinjection hours (PIH) 0, 1, 1.5, 2, 5, and 8, and by arthrocentesis at PIH 24. Joint fluid samples were analyzed for nucleated cell count, protein concentration, and TNF, ***interleukin*** ***6*** (***IL*** - ***6***), IL-1, and IL-l-inhibitory activities. To monitor local inflammation, each carpus was graded semiquantitatively for swelling prior to each sample collection.

Tumor necrosis factor, IL-1, or IL-1-inhibitory activity was not detected in any synovial fluid sample collected before endotoxin/antibody was administered. However, low ***IL*** - ***6*** activity (< 100 U/ml) was found in 2 of 12 preinjection samples. In joints injected with endotoxin/control antibody mixture, maximal mean +/- SEM activities for TNF (1,019 +/- 310 U/10 ml), IL-1 (173 +/- 102 U/ml), and ***IL*** - ***6*** (10.8 +/- 3.1 x 10(4) U/ml) were observed at PIH 2, 5, and 8, respectively. Tumor necrosis factor and IL-1 activities returned to baseline values by PIH 8 and 24, respectively; however, ***IL*** - ***6*** activity remained high. Interleukin 1-inhibitory activity (27.4 +/- 2.25 IU/ml) was detected in all PIH-24 samples from control joints, but was not detected at any other time in control joints (limit of detection, 20 IU/ml).

Tumor necrosis factor activity was not detected in any synovial fluid sample from joints ***treated*** with endotoxin/eqTNF antibody. In contrast, endotoxin-induced mean synovial IL-1 and ***IL*** - ***6*** activities were not reduced significantly by eqTNF antibody. Mean IL-1-inhibitory activity (PIH 24) was higher in eqTNF antibody- ***treated*** joints (41.0 +/- 7.7 IU/ml) than in control joints, but the difference was not significant. Mean WBC count and protein concentration in control and ***treated*** joints were maximal at PIH 8. The curves for mean values of WBC count and total protein concentration were not significantly different in ***treated*** versus control joints. Swelling in each ***treated*** joint was either less than or the same as that in the opposite control joint at every time in the initial 8 PIH. There was significant (P = 0.043) difference between ***treated*** and control joints at PIH 5 and 8. These results describe a profile of synovial fluid TNF, IL-1, ***IL*** - ***6*** bioactivities, and IL-1-inhibitory activity during the initial 24 hours of synovitis induced by intra-articular administration of endotoxin in horses. Our eqTNF monoclonal antibody was effective in neutralizing TNF activity in synovial fluid when administered intra-articularly with endotoxin in horses. The induction of IL-1, IL-1-inhibitory activity, ***IL*** - ***6*** , WBC, and total protein concentration responses are largely independent of TNF activity in synovial fluid of horses receiving endotoxin intra-articularly.

L26 ANSWER 11 OF 23 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.DUPLICATE

TI Circulating levels of interleukin 1.beta. and of interleukin 1 receptor ***antagonist*** in systemic juvenile chronic arthritis.
AU De Benedetti F.; Pignatti P.; Massa M.; Sartirana P.; Ravelli A.; Martini A.
SO Clinical and Experimental Rheumatology, (1995) 13/6 (779-884). ISSN: 0392-856X CODEN: CERHDP
AB Objective. To measure circulating interleukin 1.beta. (IL-1.beta.) and IL-1 receptor ***antagonist*** (IL-1Ra) levels in patients with systemic juvenile chronic arthritis (JCA) and to evaluate their correlation with disease activity. Methods. IL-1.beta. and IL-1Ra levels were measured by ELISA in 45 patients with JCA (20 systemic, 10 polyarticular and 15 pauciarticular) and in 15 healthy controls. Results. Plasma IL-1.beta. levels were undetectable in the majority of patients with systemic JCA, and detectable levels were not associated with different ***treatments*** or with parameters of disease severity. Serum IL-1Ra levels were markedly increased in patients with systemic JCA and significantly correlated with the persistence of systemic features, the extent and severity of joint involvement, and with C-reactive protein concentrations. Serum IL-1Ra levels were also significantly correlated with ***IL*** - ***6*** levels. Conclusion. These results argue against a relevant role of IL-1 in systemic JCA. The increase in IL-1Ra levels does not appear to reflect an increase in IL-1 production, but may rather be induced by ***IL*** - ***6*** .

L26 ANSWER 12 OF 23 MEDLINE DUPLICATE 3
TI Effect of methotrexate alone or in combination with sulphasalazine on the production and circulating concentrations of cytokines and their ***antagonists*** . Longitudinal evaluation in patients with ***rheumatoid*** ***arthritis*** .
AU Barrera P; Haagsma C J; Boerbooms A M; Van Riel P L; Borm G F; Van de Putte L B; Van der Meer J W
SO BRITISH JOURNAL OF RHEUMATOLOGY, (1995 Aug) 34 (8) 747-55.
Journal code: B1T. ISSN: 0263-7103.
AB In a recent study from our group, the combination of methotrexate and sulphasalazine (MTX + SASP) seemed superior to MTX alone in the ***treatment*** of ***rheumatoid*** ***arthritis*** (RA). To assess the impact of these therapies on the cytokine cascade, the in vitro production and circulating concentrations of several cytokines and endogenous cytokine ***antagonists*** were measured in 30 healthy controls and longitudinally in a subset of 26 patients enrolled in this study. Compared to controls, RA patients had significantly higher circulating concentrations of ***interleukin*** - ***6*** (***IL*** - ***6***), soluble receptors for tumour necrosis factor (sTNFR), soluble receptors for interleukin-2 (sIL-2R) and interleukin-1 receptor ***antagonists*** (IL-1RA), and their peripheral blood mononuclear cells (PBMNC) showed a higher spontaneous production of interleukin-1 beta (IL-1 beta), tumour necrosis factor alpha (TNF alpha) and IL-1RA (both secreted and cell-associated) and a higher stimulated production of cell-associated TNF alpha, IL-1RA and (to a lesser extent) IL-1 beta. ***Treatment*** with MTX alone (n = 12) or combined with SASP (n = 14), resulted in significant reductions of circulating ***IL*** - ***6*** and sIL-2R but did not alter IL-1 beta, TNF alpha or IL-1RA concentrations. Decreases in circulating levels of sTNFR and in the in vitro production of cell-associated IL-1 beta and IL-1RA after stimulation were only observed in patients ***treated*** with MTX + SASP. The concentrations of IL-1RA and sTNFR in the circulation exceeded moderately those of IL-1 beta and TNF alpha but this is probably insufficient to block IL-1 and TNF alpha activity. In conclusion, therapy with MTX alone or with SASP modulates ***IL*** - ***6*** and sIL-2R concentrations in RA. Decreased production of IL-1 beta and IL-1RA and circulating sTNFR levels were only observed during therapy with MTX + SASP. Whether this relates to the better clinical effect observed with the combination therapy remains to be investigated. Circulating levels of ***IL*** - ***6*** , sIL-2R and sTNFR seem useful markers of disease activity in RA.

L26 ANSWER 13 OF 23 SCISEARCH COPYRIGHT 1997 ISI (R)
TI MONOCLONAL-ANTIBODY THERAPY OF INFLAMMATORY RHEUMATIC DISEASES
AU BREEDVELD F C (Reprint); VANDERLUBBE P A
SO BRITISH MEDICAL BULLETIN, (APR 1995) Vol. 51, No. 2, pp. 493-502.
ISSN: 0007-1420.
AB The recognition that certain monoclonal antibodies have immunosuppressive properties led to the therapeutic application in autoimmune rheumatic diseases, ***rheumatoid*** ***arthritis*** in particular, The therapeutic potential of monoclonal antibodies directed against cell surface antigens mainly present on T-cells has been suggested by open trials in ***rheumatoid*** ***arthritis*** but the results of controlled studies are disappointing. Open intervention studies with monoclonal antibodies directed at other antigens relevant for the rheumatoid inflammation such as the intercellular adhesion molecule ICAM-1 or the cytokines ***IL*** - ***6*** and TNF alpha, provided encouraging clinical improvements. The impressive potential of anti-TNF alpha which was already illustrated by the immediate suppression of the acute phase response in open studies could be confirmed by a recently completed controlled trial. The present overview summarizes the available information on the results of these ***treatment*** modalities and discusses the possibilities of monoclonal antibodies as a long term ***treatment*** for rheumatic diseases.

L26 ANSWER 14 OF 23 MEDLINE DUPLICATE 4
TI Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF-alpha antibody with the interleukin-1 receptor ***antagonist*** .
AU Butler D M; Maini R N; Feldmann M; Brennan F M
SO EUROPEAN CYTOKINE NETWORK, (1995 Jul-Dec) 6 (4) 225-30.
Journal code: A56. ISSN: 1148-5493.
AB While there is an extensive literature on cytokine regulation in vivo using human cell lines or peripheral blood monocytes, very little is known about cytokine regulation within the multicellular environment of inflammatory sites in vivo. We have previously shown that in rheumatoid synovial membrane cultures, a complex, but pathophysiologically relevant mixture of cells, the addition of a neutralizing anti TNF-alpha antibody inhibits the production of IL-1 and GM-CSF, indicating the presence of a cytokine 'cascade' in this inflammatory tissue. In this paper we demonstrate that the interactivities between cytokines in ***rheumatoid*** ***arthritis*** also extends to other cytokines, such as ***IL*** - ***6*** and IL-8, and that within the IL-1 family it is IL-1 beta in particular which is downregulated by neutralizing TNF-alpha activity. The cytokine interactions are unidirectional, in that neutralization of TNF-alpha reduced IL-1 beta, ***IL*** - ***6*** and IL-8 production, whereas ***treatment*** of the rheumatoid synovial membrane cells with a neutralizing concentration of the IL-1 receptor ***antagonist*** (IL-1ra) reduced ***IL*** - ***6*** and IL-8 production but not TNF-alpha production. These results suggest a rationale for the profound anti-inflammatory effects and consequent clinical benefit noted in RA patients ***treated*** recently in clinical trials with a chimeric anti-TNF-alpha antibody in vivo.

L26 ANSWER 15 OF 23 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 5
TI Role of interleukin-1, tumor necrosis factor alpha, and ***interleukin*** - ***6*** in cartilage proteoglycan metabolism and destruction.
AU Van De Loo F A J; Joosten L A B; Van Lent P L E M; Arntz O J; Van Den Berg W B
SO Arthritis & Rheumatism 38 (2). 1995. 164-172. ISSN: 0004-3591
AB Objective: To determine the involvement of interleukin-1 (IL-1), tumor necrosis factor (TNF), and ***IL*** - ***6*** in the cartilage pathology of murine antigen-induced arthritis (AIA) and zymosan-induced arthritis (ZIA). Methods: Arthritis was induced by intraarticular injection of zymosan in naive mice or by subcutaneous injection of methylated bovine serum albumin in sensitized animals. Mini-osmotic pumps releasing human recombinant IL-1 receptor ***antagonist*** (IL-1ra) protein were implanted intraperitoneally 2 days before arthritis induction, and neutralizing antibodies directed against murine IL-1-alpha, IL-1-beta, TNF-alpha, or ***IL*** - ***6*** were administered 1 day before. Proteoglycan (PG) synthesis and degradation were assessed in patellar cartilage.

Results: Murine IL-1-alpha and IL-1-beta injected intraarticularly at doses of 0.1-100 ng suppressed chondrocyte PG synthesis. The highest dose of TNF tested (100 ng) decreased PG synthesis marginally. In contrast, the maximum dose of ***IL*** - ***6*** (1 mu-g) stimulated PG synthesis 2 days after injection. ***Treatment*** of AIA with neutralizing monoclonal antibodies against either TNF-alpha or ***IL*** - ***6*** did not reduce either the PG degradation or the suppression of its synthesis. However, ***treatment*** with anti-IL-1 (alpha + beta) polyclonal antibodies totally prevented PG suppression, although the initial breakdown of PG was unaffected. This effect was confirmed when IL-1ra was administered in high doses. Moreover, ***treatment*** of ZIA with anti-IL-1 (alpha + beta), but not with anti-TNF, resulted in normal PG synthesis, confirming the key role played by IL-1 in the inhibition of PG synthesis. ***Treatment*** of AIA with anti-IL-1 did not affect inflammation during the acute phase, but a significant reduction of ongoing inflammation was noted at day 7, and there was a marked reduction in the loss of cartilage PG. Conclusion: The suppression of PG synthesis in both ZIA and AIA in mice is due to the combined local action of IL-1 (alpha + beta), and neither ***IL*** - ***6*** nor TNF is involved. Moreover, the normalization of PG synthesis brought about by blocking of IL-1 ameliorates the cartilage damage associated with AIA.

L26 ANSWER 16 OF 23 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.

TI Inhibition of the production and effects of interleukin-1 and tumor necrosis factor .alpha. in ***rheumatoid*** ***arthritis*** .

AU Arend W.P.; Dayer J.-M.

SO Arthritis and Rheumatism, (1995) 38/2 (151-160).
ISSN: 0004-3591 CODEN: ARHEAW

AB This review has summarized information published over the last 5 years on the presence and pathophysiologic role of IL-1 and TNF.alpha. in RA. The evidence to date shows that 5 of 6 criteria for identifying mediators of tissue damage in human auto-immune diseases are satisfied (Table 1). The last criterion, prevention of clinical progression in patients with RA, is currently being evaluated. Many new therapeutic approaches are currently being developed, including the use of soluble receptors to IL-1 or TNF, monoclonal antibodies to TNF.alpha., a specific IL-1 receptor ***antagonist*** , and gene therapy with the latter molecule. It should be emphasized that both IL-1 and TNF.alpha. play important roles in normal host defense; the possible complications of blocking their production or effects need to be carefully evaluated in long-term studies. A recent review has emphasized that although IL-1 and TNF.alpha. have many overlapping biologic properties, each may exhibit distinct effects in joint disease (99). Anti-TNF ***treatment*** may be primarily antiinflammatory but blocking IL-1 may be more effective in preventing cartilage destruction (100). The possibility exists that simultaneous inhibition of TNF.alpha. and IL-1 may be more therapeutically efficacious than blockade of either agent alone, as was recently demonstrated with IL-1 ra and soluble TNF receptors in bacterial cell wall-induced arthritis in rats (101). The next level of clinical studies in ***rheumatoid*** ***arthritis*** should include the use of two biologic response modifiers together, or one agent combined with a more traditional form of therapy.

L26 ANSWER 17 OF 23 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.

TI Circulating concentrations and production of cytokines and soluble receptors in ***rheumatoid*** ***arthritis*** patients: Effects of a single dose methotrexate.

AU Barrera P.; Boerbooms A.M.Th.; Demacker P.N.M.; Van De Putte L.B.A.; Gallati H.; Van der Meer J.W.M.

SO British Journal of Rheumatology, (1994) 33/11 (1017-1024).
ISSN: 0263-7103 CODEN: BJRHDF

AB Methotrexate (MTX) is an effective ***treatment*** for RA and its effects may be partly due to cytokine modulation. Herein, we assessed the effects of a single MTX dose on the production and circulating concentrations of several cytokines and soluble receptors in 42 RA patients on three consecutive days. Three patient groups were studied: (a) 16 patients taking the first MTX dose, (b) 11 patients on chronic MTX ***treatment*** and (c) a control group of 15 patients not ***treated*** with MTX. Cytokine production was studied in peripheral blood mononuclear cells (PBMNC) and in a whole-blood culture system (WBCS). Group (a) had a more active disease according to laboratory parameters as well as higher circulating ***IL*** - ***6*** levels (P = 0.002). The secretion of IL-1.beta. by stimulated PBMNC (P = 0.008) was higher in this group and decreased significantly (P = 0.03) after a single MTX dose. No significant change in any parameter was observed after MTX in group (b). In the total patient group, circulating concentrations of IL-1.beta. and TNF-.alpha. were low but blood cells showed a high capacity of production for these cytokines. In contrast for sTNFRs, high circulating levels but a limited in vitro production were observed. In conclusion, a single MTX dose may result in decreased production of IL-1.beta. by PBMNC in patients with active RA. Furthermore, we observed an imbalance in the production of TNF-.alpha. and sTNFRs by peripheral blood cells of RA patients and propose that the WBCS is convenient for studying cytokine production in RA.

L26 ANSWER 18 OF 23 SCISEARCH COPYRIGHT 1997 ISI (R)

TI INTRAMUSCULAR GOLD DECREASES CYTOKINE EXPRESSION AND MACROPHAGE NUMBERS IN THE RHEUMATOID SYNOVIAL-MEMBRANE

AU YANNI G (Reprint); FARAHAT M N M R; POSTON R N; PANAYI G S

SO ANNALS OF THE RHEUMATIC DISEASES, (MAY 1994) Vol. 53, No. 5, pp. 315-322.
ISSN: 0003-4967.

AB Objectives-Cytokines, released from mononuclear cells (MNC) are mediators of joint destruction in ***rheumatoid*** ***arthritis*** (RA). The mechanisms of action of gold salts used in the ***treatment*** of RA are unknown. The aim of this study was to investigate cytokine expression and intensity of MNC infiltrate in the RA synovial membrane (SM) following ***treatment*** with sodium aurothiomalate (SAT).

Methods-Sequential blind needle biopsies were obtained at entry into the study and at two and 12 weeks after the start of SAT therapy in 10 patients with active RA. SMs were stained with a panel of monoclonal antibodies to assess cytokine expression (IL-1 alpha, IL-1 beta, TNF-alpha, ***IL*** - ***6*** , and GM-CSF).

Results-There was a significant decrease in IL-1 alpha, IL-1 beta, ***IL*** - ***6*** and TNF-alpha expression 12 weeks after ***treatment*** ($p < 0.004$, $p < 0.002$, $p < 0.009$ and $p < 0.004$ respectively). This was noted in the lining layer, the perivascular aggregates and the connective tissue areas. Detailed examination ofthe MNC infiltrate showed a significant reduction in inflammatory monocytes (MONO) in the lining layer at two weeks ($p < 0.03$). A decrease in the number of CD68+ macrophages (MAC) was noted in the perivascular and connective tissue areas at 12 weeks. No significant changes were observed in the number of T and B cells and blood vessels.

Conclusion-The results suggest that gold may suppress RA disease activity by diminishing MONO and MAC numbers and consequently monokine production in the SM.

L26 ANSWER 19 OF 23 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.DUPLICATE 6

TI Cytokine reduction in the ***treatment*** of joint conditions.

AU Sipe J.D.; Martel-Pelletier J.; Otterness I.G.; Pelletier J.-P.

SO MEDIATORS INFLAMM., (1994) 3/4 (243-256).
ISSN: 0962-9351 CODEN: MNFLEF

AB The destruction of joints caused by ***rheumatoid*** ***arthritis*** and osteoarthritis is characterized by an imbalance of enzyme catalysed cartilage breakdown and regeneration. A complex cytokine network perpetuates joint conditions by direct regulation of metalloproteases, by indirect recruitment of cells that secrete degradative enzymes, and by inhibition of reparative processes. The destructive action of cytokines such as interleukin-1, ***interleukin*** - ***6*** and tumour necrosis factor-.alpha. can be modulated at multiple points associated either with cytokine production or with cytokine action. Potential agents for cytokine reduction include selective anti-cytokine antibodies, anti-cytokine receptor antibodies, cytokine receptor ***antagonist*** proteins, and soluble and chimeric cytokine receptor molecules. Pharmacologic regulation of IL-1 and TNF.alpha.

remain primary targets for ***treatment*** of arthritis, and results of early clinical trials are promising. However, the results of long-term clinical trials will be required to support the value of anti-cytokine therapy in ***treatment*** of arthritis.

L26 ANSWER 20 OF 23 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.DUPLICATE 7

TI Monoclonal antibody based enzyme-linked and chemiluminescent assays for the human interleukin-1 receptor ***antagonist*** . Application to measure hIL-1ra levels in monocyte cultures and synovial fluids.

AU Towbin H.; Schmitz A.; Van Oostrum J.; Seitz M.; Dewald B.; Zingel O.; Motz J.; Vosbeck K.; Rordorf C.

SO J. IMMUNOL. METHODS, (1994) 170/1 (125-135). ISSN: 0022-1759 CODEN: JIMMBG

AB Interleukin-1 receptor ***antagonist*** (IL-1ra) has the potential to counteract at least part of the biological effects of interleukin-1. The outcome of an inflammatory reaction may therefore be determined by the balance between IL-1 and IL-1ra, rather than by IL-1 alone. We have developed an immunoassay to address this issue as well as to assess the effects of anti-inflammatory agents on the expression of IL-1 and IL-1ra in vitro or in body fluids. Recombinant human IL-1ra was expressed in an E. coli system, purified to homogeneity, and used to derive monoclonal antibodies in mice as well as polyclonal antibodies in rabbits. A sandwich ELISA was constructed with F(ab')2 fragments of a high affinity monoclonal antibody and the rabbit serum as a source of secondary antibody. The assay required no sample ***treatment*** to avoid interference by rheumatoid factor. The measuring range was 0.020-2 ng/ml. By labelling a second monoclonal antibody with an acridinium ester, a chemiluminescence assay with a wider measuring range (0.050-15 ng/ml) was generated. In accord with published data, we found that IL-1ra was secreted by human monocytes stimulated with LPS, Zymosan, IL-1.alpha., or human IgG. After an induction phase of ca. 4 hours and depending on the stimulus, IL-1ra accumulated linearly for periods up to 96 h. IL-1ra levels in synovial fluids of 19 patients suffering from various inflammatory joint diseases were compared with the cytokine levels of IL-1.beta., ***IL*** - ***6*** , IL-8, and TNF-.alpha.. Highest positive correlations were found with IL-8 and IL-1.beta.. In normal blood donors IL-1ra serum levels were 150-800 pg/ml (Median: 387 pg/ml). Owing to its sensitivity and large measuring range the newly developed assays appear to be suitable for measuring IL-1ra in cell cultures as well as in biological fluids.

L26 ANSWER 21 OF 23 MEDLINE

TI Serum levels of ***interleukin*** - ***6*** and tumour-necrosis-factor-alpha are not correlated to disease activity in patients with ***rheumatoid*** ***arthritis*** after ***treatment*** with low-dose methotrexate.

AU Wascher T C; Hermann J; Brezinschek R; Brezinschek H P; Wilders-Truschnig M; Rainer F; Krejs G J

SO EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, (1994 Jan) 24 (1) 73-5. Journal code: EN3. ISSN: 0014-2972.

AB Cytokines are major mediators of inflammatory responses in ***rheumatoid*** ***arthritis*** . Some of them have been shown to correlate with the disease activity and thus are proposed to be used for monitoring patients. Therefore the effects of a low-dose therapy with methotrexate on serum concentrations of ***interleukin*** - ***6*** (***IL*** - ***6***) and tumour-necrosis-factor-alpha (TNF-alpha) were examined in eight patients with seropositive ***rheumatoid*** ***arthritis*** . Serum levels of ***IL*** - ***6*** and TNF-alpha were significantly elevated in patients compared to healthy controls. Before the onset of MTX ***treatment*** ***IL*** - ***6*** concentrations were correlated to the c-reactive protein ($P < 0.05$) but the correlation was abolished after ***treatment*** . For TNF-alpha no correlations neither before nor after ***treatment*** were observed. Both cytokines remained substantially elevated after MTX ***treatment*** despite a clear reduction in disease activity. Thus we suggest that one of the effects of MTX might be the inhibition of some of the actions of ***IL*** - ***6*** and TNF-alpha.

L26 ANSWER 22 OF 23 SCISEARCH COPYRIGHT 1997 ISI (R)

TI THE INVOLVEMENT OF BRADYKININ B-1 AND B-2 RECEPTOR MECHANISMS IN CYTOKINE-INDUCED MECHANICAL HYPERALGESIA IN THE RAT

AU DAVIS A J; PERKINS M N (Reprint)

SO BRITISH JOURNAL OF PHARMACOLOGY, (SEP 1994) Vol. 113, No. 1, pp. 63-68. ISSN: 0007-1188.

AB 1 Interleukin-1 beta (IL-1 beta), IL-2 and IL-8 induced a mechanical hyperalgesia Following intra-articular (i.artic.) injection into rat knee joints, whereas ***IL*** - ***6*** and tumour necrosis factor alpha (TNF-alpha) were without effect.

2 Co-administration of IL-1 receptor ***antagonist*** (0.1 mu g) with IL-1 beta (1 u), IL-2 (10 u) or IL-8 (0.1 u) prevented the subsequent development of the hyperalgesia.

3 Co-administration of desArg(9)Leu(8)BK (0.5-5 nmol) with IL-1 beta (1 u), IL-2 (10 u) or IL-8 (0.1 u) reduced the level of hyperalgesia at 1, 4 and 6 h post administration, whereas Hoe 140 (5 pmol) antagonized the hyperalgesia only at the 1 h time point.

4 Intravenous administration of desArg(9)Leu(8)BK (10 nmol kg(-1)) or Hoe 140 (100 pmol kg(-1)) following IL-1 beta (1 u), IL-2 (10 u), or IL-8 (0.1 u) reversed the subsequent hyperalgesia.

5 Administration of desArg(9)BK into joints 24 h after pre- ***treatment*** with IL-1 beta (1 u) produced analgesia at low doses (50 pmol) and hyperalgesia at a higher dose (0.5 nmol). Both these effects were blocked, by desArg(9)Leu(8)BK (0.5 nmol).

6 Administration of desArg(9)BK (0.5 nmol i.artic.) to animals 24 h after pre- ***treatment*** with IL-2 (1-100 u) or IL-8 (0.1-10 u) had no effect on the load tolerated by the ***treated*** joint.

7 Administration of indomethacin (1 mg kg(-1), s.c.) prior to IL-1 beta (1 u i.artic.) prevented the development of hyperalgesia. Administration of desArg(9)BK (5 pmol-0.5 nmol, i.artic.) to animals 24 h after indomethacin and IL-1 beta pretreatment had no effect on the load tolerated by the ***treated*** joint.

8 These data suggest that both bradykinin B-1 and B-2 receptors are involved in the induction and maintenance of cytokine-induced hyperalgesia. They also show that the induction of B-1 receptor-mediated hyperalgesia requires both cyclo-oxygenase products and IL-1 in vivo.

L26 ANSWER 23 OF 23 EMBASE COPYRIGHT 1997 ELSEVIER SCI. B.V.

TI Regulation of expression of IL-1 receptor ***antagonist*** protein in human synovial and dermal fibroblasts.

AU Krzesicki R.F.; Hatfield C.A.; Bienkowski M.J.; McGuire J.C.; Winterrowd G.E.; Chapman D.L.; Berger A.E.; McEwan R.N.; Carter D.B.; Chosay J.G.; Tracey D.E.; Jia En Chin

SO J. IMMUNOL., (1993) 150/9 (4008-4018). ISSN: 0022-1767 CODEN: JOIMA3

AB The IL-1R ***antagonist*** protein (IRAP) is a competitive inhibitor of IL-1, which is predominantly synthesized by monocytes. We show that this molecule is also expressed in human synovial fibroblasts and dermal fibroblasts (CRL 1445). IRAP mRNA was regulated in a time- and dose-dependent manner by IL- 1.alpha., TNF-.alpha., LPS, and PMA. Maximal induction of IRAP mRNA was observed between 8 and 16 h after stimulation with IL-1.alpha. (1 U/ml), TNF-.alpha. (10 U/ml), LPS (50 ng/ml), and PMA (10 ng/ml). Their relative efficacy was as follows: PMA > LPS > IL-1.alpha. > TNF-.alpha.. Potentiation was observed when fibroblasts were ***treated*** with IL-1.alpha. plus basic fibroblast growth factor and IL-1.alpha. plus platelet-derived growth factor-BB homodimer. Although LPS and PMA were the best inducers of IRAP mRNA, quantitation of the IRAP protein revealed that its synthesis and release were differentially regulated. Immunoprecipitation and SDS-PAGE of culture supernatant from LPS- ***treated*** cells and cell lysates of fibroblasts ***treated*** with LPS or PMA showed a single IRAP band with a molecular mass of .apprx.22 kDa. Very little IRAP was detected in culture supernatants of cells ***treated*** with PMA. Quantitation of IRAP revealed that LPS induced the synthesis of secreted IRAP that was released, whereas the majority of the protein induced by PMA remained cell-associated. Reverse transcriptase-polymerase chain reaction amplification

demonstrated that although LPS and PMA induced both transcripts, LPS preferentially induced secreted IRAP, whereas PMA differentially induced intracellular IRAP mRNA. Fibroblasts synthesize at least two different forms of IRAP depending on the inducing signal, and may regulate the inflammatory response by dampening the proinflammatory effects of IL-1 via a negative feedback mechanism with IRAP. The relative importance of fibroblast sIRAP vs intracellular IRAP in regulating the inflammatory response by the connective tissue remains to be determined.

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L25 ANSWER 1 OF 1 MEDLINE
TI New directions for biological therapy in ***rheumatoid*** ***arthritis*** .
AU Elliott M J; Maini R N
SO INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (1994) 104 (2)
112-25. Ref: 90
Journal code: BJ7. ISSN: 1018-2438.
AB Advances in our understanding of the pathogenesis of ***rheumatoid*** ***arthritis*** (RA), together with developments in hybridoma and molecular technology have opened the way for more directed therapy in this disease. In reviewing the experience so far with T-cell-directed biological agents, we show that the early promise displayed by anti-CD4 monoclonal antibodies in open clinical trials has not been sustained in controlled studies. This outcome provides a challenge to the concept that CD4+ T cells are of prime importance in RA, and prompts a search for alternative therapeutic targets. Agents directed towards other leucocyte antigens such as CD5, CDw52 or the receptor for interleukin 2 have induced clinical responses in early studies, but at the expense of significant toxicity. Newer therapies targeting the monokines tumour necrosis factor alpha (TNF-alpha), IL-1 and ***IL*** - ***6*** , and the leucocyte adhesion molecule intercellular adhesion molecule 1 (ICAM-1) have provided encouraging clinical improvements and, in the case of anti-TNF-alpha and ***anti*** - ***IL*** - ***6*** , impressive modulation of the acute-phase response. Strategies allowing long-term blockade of such molecules, including antibody reshaping and the use of soluble cytokine receptors are discussed. Finally, the potential for using biological agents in combination with other therapies is outlined.

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